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Original article

Sleep apnea and ventricular arrhythmias: Clinical outcome, electrophysiologic characteristics, and follow-up after catheter ablation

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Summary
Background and objectives: Sleep apnea is highly prevalent in patients with heart disease. However, the association between sleep apnea and ventricular arrhythmias is unclear. The aim of this study was to examine the relationship between sleep apnea and electrophysiologic characteristics and clinical outcome after catheter ablation in patients having ventricular arrhythmias.
Methods and results: Forty-four patients with ventricular tachycardia (VT) or premature ventricular complexes (PVCs) without structural heart diseases (57% men; mean age: 55 ± 15 years) underwent a sleep study. Subjects with an apnea—hypopnea index (AHI) ≥10/h were considered to have sleep apnea. Electrophysiologic studies were performed on all patients, and 35 patients underwent catheter ablation therapy. Seventeen patients (39%) had sleep apnea with an average AHI of 27 ± 17/h. Electrophysiologic characteristics of ventricular arrhythmias showed that sites of VT/PVCs origin in the pulmonary artery and the aortic sinus of Valsalva were detected in 27% and 20% patients with sleep apnea, which was a relatively higher rate than that in patients without sleep apnea (8% and 0%, respectively). Successful catheter ablation was achieved in 11 patients (85%) with sleep apnea and 17 (77%) without sleep apnea. During a mean follow-up period of 13.5 ± 7.3 months after catheter ablation, 5 patients (45%) with sleep apnea and 1 patient (6%) without sleep apnea experienced recurrent VT/PVCs. Comparing the outcome

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between the two groups, the VT/PVCs recurrence rate was significantly higher in patients with sleep apnea than in those without sleep apnea ($p = 0.02$).
Conclusions: Ventricular arrhythmia patients with sleep apnea have a high recurrence of arrhythmias after successful catheter ablation. Patients with ventricular arrhythmias should be systematically assessed for sleep apnea owing to the potential detrimental effects of sleep apnea in the follow-up period.

Introduction

Sleep apnea is associated with heart diseases such as atrial fibrillation [1], ischemic heart disease [2], and heart failure [3]. A recent epidemiologic study reported a significant increase in the prevalence of nocturnal atrial fibrillation, nonsustained ventricular tachycardia (VT), and premature ventricular complexes (PVCs) in subjects with severe sleep apnea compared to those without sleep apnea [4,5]. Furthermore, a previous study reported that sleep apnea patients have a significantly increased risk of cardiac-related sudden death between midnight and 06.00 h [6,7]. Another report showed that patients with untreated sleep apnea have a higher risk of recurrence of atrial fibrillation after successful cardioversion than those without known sleep apnea [8]. However, limited data exist on the relationship between sleep apnea and ventricular arrhythmias.

Ventricular arrhythmias constitute a relatively small and distinct subset, occurring in patients even without detectable underlying heart disease. Detailed clinical observations and electrophysiologic studies led to a differentiation of VT into 'repetitive monomorphic VT,' 'nonsustained VT,' and 'frequent PVCs.' Recently, radiofrequency catheter ablation has been shown to be an effective and safe treatment modality for idiopathic VT. However, the underlying mechanism of idiopathic VT is still a matter of debate because controversial findings have been reported in a limited number of patients [9,10]. Although sporadic reports have attempted to implicate hypoxia as one of the mechanisms of cardiac arrhythmias in humans [11], there is a lack of convincing proof to verify this claim.

The aim of this study was to examine the relationship between sleep apnea and electrophysiologic characteristics and follow-up after catheter ablation in patients having VT without structural heart disease.

Materials and methods

Study population

Between April 2004 and October 2007, 90 consecutive patients (50% men; mean age: 49 ± 18 years) with VT or PVCs were referred to the Cardiology Department of Tsukuba University Hospital, Tsukuba, Japan, for catheter ablation. The selection criteria for catheter ablation included potentially fatal arrhythmias or severe symptoms that were clearly related to frequent ventricular arrhythmias, inability of the patient to tolerate treatment, or unsuccessful treatment with at least two antiarrhythmic drugs. The study group in the present study consisted of 44 of the 90 patients. Study subjects were randomly selected from among the patients who were older than 20 years and who did not have any history of myocardial infarction, heart failure, valvular heart disease, cardiomyopathy, obstructive lung disease, clinical signs of central or peripheral nervous system impairment, or history of stroke. Initial assessment included historic data collection, routine blood tests, 12-lead electrocardiography, and echocardiography. Sustained VT was defined as VT lasting more than 30 s or causing hemodynamic deterioration necessitating intervention to terminate the VT. Nonsustained VT was defined as three or more consecutive ventricular beats lasting less than 30 s and without hemodynamic instability. The presence of coronary artery disease (>75% stenosis of any major epicardial vessel) was assessed by stress testing and/or cardiac catheterization. Subjective sleepiness was assessed using Epworth Sleepiness Scale, which is a validated 8-item self-administered questionnaire [12]. Written informed consent was obtained from all subjects, and the study protocol was approved by the Ethical Committee of the University of Tsukuba.

Sleep studies

Sleep evaluations of all 44 subjects were conducted by a sleep specialist 2 days after the electrophysiologic study with standard sleep studies, which were performed by monitoring of electroencephalogram, electrooculogram, electromyogram, electrocardiogram, thoracoabdominal excursions, pulse oximetry, and naso-oral airflow using Alice 4 (Respironics, Pittsburgh, PA, USA).

Apnea was defined as cessation of inspiration for at least 10 s. All such events were counted irrespective of the degree of desaturation. Hypopnea was defined as a reduction in airflow by at least 30% with a decrease in oxygen saturation (SaO_2) by 4% or more for at least 10 s. The apnea–hypopnea index (AHI) was calculated as the sum of apneic and hypopneic events per hour of sleep. An AHI threshold ≥10/h was used for the diagnosis of sleep apnea.

Electrophysiologic study and catheter ablation

All patients underwent an invasive electrophysiologic study in the fasting, unsedated state. Antiarrhythmic agents were discontinued for at least five half-lives before the study. Three quadripolar electrode catheters were inserted percutaneously into the femoral vein and advanced to the right ventricle under fluoroscopic guidance. These three catheters were used to record intracardiac local electrograms and to stimulate at the right ventricular apex (RVA), the right ventricular outflow tract (RVOT), and the His bundle area. A decapolar electrode catheter was also inserted into the very distal coronary sinus. The protocol for premature ventricular stimulation was to apply up to three extrastimuli at two basic cycle lengths of 600 and 400 ms.

Ventricular burst pacing was applied for 20 beats at cycle lengths of 250—400 ms at the RVA and RVOT. Mapping and ablation were carried out with a deflectable quadripolar catheter with 4-mm distal tip electrode. Both right and left ventricular endocardial activation mapping during tachycardia and pace mapping during sinus rhythm were performed in the right and left ventricles to localize the sites of VT origin. In some patients, an electroanatomical mapping system (CARTO, Biosense Webster, Inc., Diamond Bar, CA, USA) was used for endocardial activation mapping to more precisely identify the origin of tachyarrhythmias. Catheter ablation was performed on 35 patients by applying radiofrequency energy at the site where endocardial activation was the earliest and where pace mapping displayed a QRS complex matched to that of spontaneous VT/PVCs. Successful ablation was defined as complete abolition of sustained VT or repetitive PVCs for at least 90 min after intravenous infusion of isoproterenol, adenosine triphosphate, or edrophonium. Recurrences of VT/PVCs were originated from the same focus, which were assessed by clinical symptoms, electrocardiogram, and the detection of more than 1500 beats/day on 24-h Holter recordings at a follow-up visit between 1 and 2 months after catheter ablation.

Statistical analysis

Results are expressed as mean ± SD. Comparisons of continuous variables between groups were made with unpaired *t*-tests where appropriate and otherwise with the Mann—Whitney test. Categorical variables were compared by Fisher's exact test or the χ^2 test, depending on appropriateness. Values with $p < 0.05$ were considered significant. The odds ratio (OR) and 95% confidence intervals (CI) for the association between recurrence of VT/PVCs were assessed by univariate logistic regression.

Results

Baseline data

Sleep apnea was found in 17 of 44 patients (39%). In 6 of these patients (14%), severe sleep apnea (AHI ≥30/h) was observed. The clinical characteristics of both groups are summarized in Table 1. The mean age of this cohort was 55 ± 15 years old, 57% were men, and mean body mass index (BMI) was 24.1 ± 3.8 kg/m^2. Gender difference between patients with and without sleep apnea was not statistically significant. Patients with sleep apnea were older than those without sleep apnea (60 ± 15 years vs 52 ± 14 years, $p = 0.02$), and their BMI and waist circumference were significantly higher than those of patients without sleep apnea (BMI, 27.0 ± 3.8 kg/m^2 vs 22.3 ± 2.9 kg/m^2, $p < 0.01$; waist circumference, 94 ± 10 cm vs 80 ± 9 cm, $p < 0.01$). Systolic blood pressure was significantly higher in sleep apnea patients (127 ± 7 mmHg vs 118 ± 12 mmHg, $p < 0.01$), whereas no differences were found in diastolic blood pressure and the rate of hypertension. The echocardiographic left ventricular end-diastolic dimension was significantly larger in patients with sleep apnea than in patients without sleep apnea (51 ± 3 cm vs 48 ± 6 cm, $p = 0.03$), whereas no differences were found in the left ventricular end-systolic dimension or the left ventricular ejection fraction. There

Table 1 Patient characteristics.

	Sleep apnea ($n = 17$)	No sleep apnea ($n = 27$)	*p*-Value
Male, *n* (%)	11 (65)	13 (48)	0.4
Age (years)	60 ± 15	52 ± 14	0.02
BMI (kg/m^2)	27.0 ± 3.4	22.3 ± 2.9	<0.01
Waist circumference (cm)	94 ± 10	80 ± 9	<0.01
Systolic blood pressure (mmHg)	127 ± 7	118 ± 12	<0.01
Diastolic blood pressure (mmHg)	72 ± 11	68 ± 11	0.1
LVEDd (cm)	51 ± 3	48 ± 6	0.03
LVESd (cm)	32 ± 4	32 ± 5	0.5
LVEF (%)	67 ± 7	64 ± 9	0.1
BNP level (pg/ml)	141 ± 322	67 ± 80	0.1
PVCs per day (*n*)	20625 ± 13625	21283 ± 21553	0.5
History			
Hypertension, *n* (%)	6 (35)	4 (15)	0.1
Hypercholesterolemia, *n* (%)	3 (18)	5 (19)	0.9
Diabetes mellitus, *n* (%)	0 (0)	1 (4)	0.4
Angina pectoris, *n* (%)	1 (6)	0 (0)	0.2
Atrial fibrillation, *n* (%)	2 (12)	3 (11)	1
Clinical classification of arrhythmia			
Sustained VT, *n* (%)	3 (18)	11 (41)	0.2
Nonsustained VT, *n* (%)	10 (59)	12 (44)	0.5
Repetitive PVCs, *n* (%)	4 (24)	4 (15)	0.5

BMI, body mass index; LVEDd, left ventricular end-diastolic dimension; LVESd, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction; BNP, B-type natriuretic peptide; PVC, premature ventricular complex; VT, ventricular tachycardia.

Table 2 Sleep study data.

	Sleep apnea ($n=17$)	No sleep apnea ($n=27$)	p-Value
AHI (n/h)	27 ± 17	4 ± 3	<0.01
OA (n/h)	10 ± 11	1 ± 1	<0.01
CA (n/h)	4 ± 5	0 ± 0	<0.01
4% ODI (n/h)	22 ± 16	4 ± 4	<0.01
Lowest SaO_2 (%)	79 ± 13	89 ± 4	<0.01
Mean SaO_2 (%)	94 ± 2	95 ± 2	0.01
Epworth sleepiness score	7.2 ± 3.8	6.2 ± 4.0	0.2

AHI, apnea—hypopnea index; OA, obstructive apnea; CA, central apnea; ODI, oxygen desaturation index.

was no difference in clinical classification of arrhythmias between the groups.

Sleep study data

The sleep study showed the mean AHI of patients with sleep apnea to be 27 ± 17/h and that of patients without sleep apnea to be 4 ± 4/h (Table 2). Comparison of patients with and without sleep apnea showed that sleep apnea patients had significantly increased 4% oxygen desaturation index (ODI) ($p<0.01$) and significantly decreased mean and lowest SaO_2 values ($p<0.01$; $p=0.01$). The Epworth sleepiness score was low in both groups and was not statistically different between the two groups (7.2 ± 3.8 in sleep apnea patients; 6.2 ± 4.0 in non-sleep apnea patients, $p=0.2$). No correlation existed between the symptoms related to sleep apnea (Epworth score) and disease severity (AHI value).

Electrophysiologic study data and outcome after catheter ablation therapy

The electrophysiologic characteristics of ventricular arrhythmias are shown in Table 3. During electrophysiologic studies, VT or PVCs were induced in 15 of 17 patients (88%) with sleep apnea and 25 of 27 patients (93%) without sleep apnea. Three patients with sleep apnea and 2 patients without sleep apnea had more than one origin of VT/PVCs. In patients with sleep apnea, sites of VT/PVCs origin were detected, 27% of them in the pulmonary artery, 47% of them in the right ventricular (RV) endocardium, 20% of them in the aortic sinus of Valsalva, and 13% of them in the left ventricular (LV) endocardium. In patients without sleep apnea, sites of VT/PVCs origin were detected, 8% of them in the pulmonary artery, 72% of them in the RV endocardium, 8% of them in the RV epicardium, 20% of them in the LV endocardium, and 4% of them in the LV epicardium. Sites of VT/PVCs origin in the pulmonary artery and the aortic sinus of Valsalva were detected in 27% and 20% patients with sleep apnea, which was a relatively higher rate than that in patients without sleep apnea (8% and 0%), but there was no statistical difference. There was no difference in the rate of other sites of VT/PVCs origin between the two groups. In 2 of 15 patients with sleep apnea and 3 of 25 patients without sleep apnea, the arrhythmias could not be eliminated by radiofrequency catheter ablation either because adequate radiofrequency energy could not be delivered safely to avoid risk, the site of earliest ventricular activation could not be determined by electrophysiologic study, or a stable position of the ablation catheter could not be maintained. In the remaining 35 patients, 11 patients (85%) with sleep apnea and 17 patients (77%) without sleep apnea were successfully treated by radiofrequency catheter ablation. During a follow-up period of 13.5 ± 7.3 months (range, 1—24 months) after hospital discharge catheter ablation, VT/PVCs recurred in 5 patients (45%) with sleep apnea and in 1 (6%) without. Comparing the outcome between the two groups, the recurrence rate of VT/PVCs was significantly higher in patients with sleep apnea than in those without ($p=0.02$). Recurrent VT/PVCs origins were LV endocardium, aortic sinus of Valsalva, and RV endocardium in 5 patients with sleep apnea and RV endocardium in 1 patient without sleep apnea. Table 4 shows that univariate analysis identified significant associations between recurrence of VT/PVCs and

Table 3 Electrophysiologic study findings and results of catheter ablation.

	Sleep apnea ($n=15$)	No sleep apnea ($n=25$)	p-Value
Mechanism			
Triggered activity, n (%)	15 (100)	21(84)	0.3
Monofocal, n (%)	13 (87)	19 (76)	0.7
Multifocal, n (%)	2 (13)	3 (12)	1
Reentry, n (%)	0 (0)	4 (16)	0.3
Site of origin			
RV endocardium, n (%)	7 (47)	18 (72)	0.2
RV epicardium, n (%)	0 (0)	2 (8)	0.5
Pulmonary artery, n (%)	4 (27)	2 (8)	0.2
LV endocardium, n (%)	2 (13)	5 (20)	0.7
LV epicardium, n (%)	0 (0)	1 (4)	1
Aortic sinus of Valsalva, n (%)	3 (20)	0 (0)	0.05
Successful ablation, n (%)	11/13 (85)	17/22 (77)	0.6
Recurrence after successful catheter ablation, n (%)	5/11 (45)	1/17 (6)	0.02

LV, left ventricle; RV, right ventricle.

Table 4 Unadjusted ORs and 95% CIs for recurrence of VT/PVCs.

	OR	95% CI	*p*-Value
Age (years old)	1.04	0.98—1.12	0.21
BMI (kg/m^2)	1.28	1.00—1.74	0.07
Waist circumference (cm)	1.13	1.02—1.28	0.03
Systolic blood pressure (mmHg)	1.02	0.94—1.11	0.57
LVEDd (cm)	1.05	0.89—1.27	0.56
LVEF (%)	1.06	0.93—1.21	0.37
AHI	1.11	1.02—1.24	0.03
4% ODI (*n*/h)	1.11	1.02—1.26	0.04
Mean SaO_2 (%)	0.96	0.66—1.38	0.06

OR, odds ratio; CI, confidence interval; VT, ventricular tachycardia; PVC, premature ventricular complex; BMI, body mass index; LVEDd, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; AHI, apnea—hypopnea index; ODI, oxygen desaturation index.

waist circumference (OR 1.13, 95% CI 1.00—1.28, $p = 0.03$), AHI (OR 1.11, 95% CI 1.02—1.24, $p = 0.03$), and 4% ODI (OR 1.11, 95% CI 1.02—1.26, $p = 0.04$).

Discussion

The novel findings of the present study are that recurrence of ventricular arrhythmias after successful catheter ablation was more likely to occur in patients with sleep apnea than in patients without sleep apnea (45% vs 6%). To our knowledge, no previous reports exist that address the recurrence of ventricular arrhythmias after catheter ablation in patients with sleep apnea. This is the first report to indicate the relationship between ventricular arrhythmias and sleep apnea on the basis of the analysis of electrophysiologic characteristics of ventricular arrhythmias and data from sleep studies. Furthermore, in this study, although 39% of the participants with sleep apnea were significantly older and had higher BMI, waist circumference, and systolic blood pressure values than those without sleep apnea as traditionally reported [13], the presence of sleep apnea in this population of patients could not be predicted according to symptoms of daytime sleepiness.

The present study revealed a higher recurrence rate of ventricular arrhythmias in patients with sleep apnea. The mechanisms by which sleep apnea predisposes a person to ventricular arrhythmias are not fully understood, but they may include two contributing factors: activation of the sympathetic nervous system induced by linkage to episodes of hypoxemia and arousal, and temporary hemodynamic alterations related to increased intrathoracic pressure changes against the occluded upper airway.

The repetitive hypoxia and reoxygenation episodes are characteristic of the patients with sleep apnea. Previous reports showed a relationship between deoxyhemoglobin and VT/PVCs [11,14,15]. Moreover, several studies reported that in sleep apnea patients with hypoxia, a significant increase in PVC frequency was detected with decreasing SaO_2 [4,16]. In patients with sleep apnea, it has been suggested that repetitive obstruction of normal breathing during sleep induces hypoxemia and hypercapnia, which (acting through the chemoreflexes) elicit increased sympathetic activity that induces VT/PVCs [17,18]. Peripheral chemoreceptors, which primarily respond to blood oxygen level, were found to be highly sensitive in patients with sleep apnea. Enhanced chemoreflex sensitivity may explain the exaggerated sympathetic response during hypoxemic episodes, resulting in autonomic activity-dependent arrhythmias [19—23].

Another characteristic in sleep apnea is frequent arousal resulting in sudden increases in sympathetic nervous activity and withdrawal of cardiac vagal activity. Those abrupt sympathetic changes induced by arousal may trigger arrhythmias [24,25]. Additionally, frequent arousal during sleeping results in sleep deprivation. Previous literature showed that sleep deprivation increases the sympathetic nervous activity in the heart and significantly increases the number of PVCs occurring during wakefulness [26—28].

Abrupt changes in intrathoracic pressure contribute to form causative substrate for occurrence of ventricular arrhythmias in patients with sleep apnea. Repetitive massive negative intrathoracic pressure is supposed to increase wall stress and acute changes of ventricular performance may also contribute to occurrence of ventricular arrhythmias. Previous literature showed that producing large negative intrathoracic pressure induced increases in left and right ventricular volume and decreases in ejection fraction due to increased left ventricular afterload [29,30]. Repetitive loaded pressure impaired not only cardiac function but also morphology and could lead to alternate the electrical conducting system in the ventricle. Consequently, the affected ventricle would become a feasible substrate for occurrence of ventricular arrhythmias.

A limitation of this study is that the sample size was small, and therefore it is possible that some of the comparisons that did not show any significant difference in the sites of VT/PVCs origin between the two groups could be due to type II statistical error. Furthermore, we found a higher incidence of aortic sinus of Valsalva in those with sleep apnea but we had 3 vs 0 patients in these groups. This is hardly sufficiently robust to allow for definitive conclusions. Second, polysomnography may provide more detailed information about sleep time and the type of sleep apnea, but in a few patients, we could not examine electroencephalograms, electrooculograms, electromyograms, or thoracoabdominal excursions to assess sleep apnea because all study patients undergoing evaluation by electrophysiologic study or catheter ablation therapy for ventricular arrhythmias had various other disease conditions. Under these circumstances, we felt that full polysomnography could impose undue stress on these patients. Nevertheless, this is a valid approach to monitoring respiratory function during sleep.

Conclusion

In conclusion, we found that ventricular arrhythmia patients with sleep apnea have a higher rate of recurrence of VT/PVCs after catheter ablation for arrhythmias compared with non-sleep apnea patients. Our data also showed that sleep apnea in patients with VT/PVCs was associated with few symptoms of daytime sleepiness. Consequently, we propose that patients with ventricular arrhythmias should be

screened for sleep apnea. Further studies are needed in these patients to define the optimal treatment strategy.

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